L Number	Hits	Search Text	DB	Time stamp
1	404	metronidazole	EPO; JPO; DERWENT	2003/01/03 10:31
2	7273	cyclodextrin	EPO; JPO; DERWENT	2003/01/03 10:31
3	504	niacin niacinamide	EPO; JPO; DERWENT	2003/01/03 10:31
4	5318	nicotinic nicotinamide	EPO; JPO; DERWENT	2003/01/03 10:31
5	2008371	water aqueous solubil$9	EPO; JPO; DERWENT	2003/01/03 10:32
6	128	(cyclodextrin (niacin niacinamide) (nicotinic nicotinamide) (water aqueous solubil$9)) and metronidazole	EPO; JPO; DERWENT	2003/01/03 10:32

L Number	Hits	Search Text	DB	Time stamp
1	1870	metronidazole	USPAT; US-PGPUB	2003/01/03 09:38
2	1056608	aqueous water solubil$9	USPAT; US-PGPUB	2003/01/03 09:39
3	187	metronidazole same (aqueous water solubil$9)	USPAT; US-PGPUB	2003/01/03 09:39
4	7770	cyclodextrin	USPAT; US-PGPUB	2003/01/03 09:39
5	13271	nicotinic nicotinamide	USPAT; US-PGPUB	2003/01/03 09:39
6	3623	niacin niacinamide	USPAT; US-PGPUB	2003/01/03 09:40
7	24505	cyclodextrin (nicotinic nicotinamide) (niacin niacinamide) metronidazole	USPAT; US-PGPUB	2003/01/03 09:40
8	187	(metronidazole same (aqueous water solubil$9)) and (cyclodextrin (nicotinic nicotinamide) (niacin niacinamide) metronidazole)	USPAT; US-PGPUB	2003/01/03 09:40

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     (FILE 'HOME' ENTERED AT 08:52:38 ON 03 JAN 2003)

     FILE 'REGISTRY' ENTERED AT 08:52:50 ON 03 JAN 2003
L1             1 S METRONIDAZOLE/CN
                 SELECT L1 1- CHEM

     FILE 'CAPLUS, MEDLINE, EMBASE, BIOSIS' ENTERED AT 08:53:58 ON 03 JAN 2003
L2         47618 S E1-32
L3         32748 DUP REM L2 (14870 DUPLICATES REMOVED)
L4         40689 S CYCLODEXTRIN
L5         86817 S NICOTINIC
L6         67402 S NICOTINAMIDE
L7         11231 S NIACIN
L8        198140 S L4 OR L5 OR L6 OR L7
L9         46716 S METRONIDAZOLE
L10        40689 S CYCLODEXTRIN
L11        86817 S NICOTINIC
L12        67402 S NICOTINAMIDE
L13        11231 S NIACIN
L14         5763 S NIACINAMIDE
L15       201186 S L10 OR L11 OR L12 OR L13 OR L14
L16          189 S L15 AND L9
L17          161 DUP REM L16 (28 DUPLICATES REMOVED)
L18       435595 S SOLUBILITY OR SOLUBILIZ?
L19      1161421 S AQUEOUS
L20      3097083 S WATER
L21      3932107 S L19 OR L20
L22           13 S L17 AND L18 AND L21
```

L22 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:72162 CAPLUS
DOCUMENT NUMBER: 136:107569
TITLE: Gel compositions containing **metronidazole** and hydroxypropyl-.beta.-**cyclodextrin**
INVENTOR(S): Chang, Yunik; Dow, Gordon J.; Angel, Arturo
PATENT ASSIGNEE(S): Dow Pharmaceutical Sciences, USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002006349	A1	20020124	WO 2001-US19644	20010619
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6468989	B1	20021022	US 2000-615169	20000713

PRIORITY APPLN. INFO.: US 2000-615169 A 20000713
AB An **aq**. soln. of **metronidazole** in which the concn. of **metronidazole** is >0.75 is described. The soln. contains the **soly**. enhancer hydroxypropyl-.beta.-**cyclodextrin** (I) and may addnl. contain **niacinamide**. Methods of manuf. and therapeutic use of the soln. are disclosed. Thus, a stable 1.0% **aq**. gel compn. contained **metronidazole** 1.00, I 5.00, methylparaben 0.15, propylparaben 0.03, glycerin 5.00, hydroxyethyl cellulose 1.50, disodium edetate 0.05, and **water** qs to 100%.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:71873 CAPLUS
DOCUMENT NUMBER: 136:123671
TITLE: Ophthalmic formulation of a selective cyclooxygenase-2 inhibitory drug
INVENTOR(S): Kararli, Tugrul T.; Bandyopadhyay, Rebanta; Singh, Satish K.; Hawley, Leslie C.
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002005815	A1	20020124	WO 2001-US22061	20010712
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002035264	A1	20020321	US 2001-904098	20010712

PRIORITY APPLN. INFO.: US 2000-218101P P 20000713
US 2001-279285P P 20010328
US 2001-294838P P 20010531
US 2001-296388P P 20010606
OTHER SOURCE(S): MARPAT 136:123671
AB A pharmaceutical compn. suitable for topical administration to an eye contains a selective COX-2 inhibitor or nanoparticles of a drug of low **water soly**., at a concn. effective for the treatment and/or prophylaxis of a disorder in the eye, and 1 or more ophthalmically acceptable excipients that reduce rate of removal from the eye such that

the compn. has an effective residence time of 2-24 h. Also provided is a method of treating and/or preventing a disorder in an eye, the method comprising administering to the eye a compn. of the invention. Thus, an ophthalmic nanoparticle suspension contained valdecoxib at 2.15 mg/g, 1.2% glycerin, 0.8% EDTA disodium salt, 4.0% Gelcarin GP-379NF, 0.21% SeaSpen PF and 0.82% Povidone.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:300514 CAPLUS
DOCUMENT NUMBER: 134:331617
TITLE: Oil-in-**water** emulsion compositions for polyfunctional active ingredients
INVENTOR(S): Chen, Feng-jing; Patel, Mahesh V.
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001028555	A1	20010426	WO 2000-US28835	20001018
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002107265	A1	20020808	US 1999-420159	19991018

PRIORITY APPLN. INFO.: US 1999-420159 A 19991018

AB Pharmaceutical oil-in-**water** emulsions for delivery of polyfunctional active ingredients with improved loading capacity, enhanced stability, and reduced irritation and local toxicity are described. Emulsions include an **aq**. phase, an oil phase comprising a structured triglyceride, and an emulsifier. The structured triglyceride of the oil phase is substantially free of triglycerides having three medium chain (C6-C12) fatty acid moieties, or a combination of a long chain triglyceride and a polarity-enhancing polarity modifier. The present invention also provides methods of treating an animal with a polyfunctional active ingredient, using dosage forms of the pharmaceutical emulsions. For example, an emulsion was prepd., with cyclosporin A as the polyfunctional active ingredient dissolved in an oil phase including a structured triglyceride (Captex 810D) and a long chain triglyceride (safflower oil). The compn. contained (by wt.) cyclosporin A 1.0, Captex 810D 5.0, safflower oil 5.0, BHT 0.02, egg phospholipid 2.4, dimyristoylphosphatidyl glycerol 0.2, glycerol 2.25, EDTA 0.01, and **water** up to 100%, resp.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:71430 CAPLUS
DOCUMENT NUMBER: 124:155977
TITLE: **Cyclodextrin** complexation
INVENTOR(S): Loftsson, Thorsteinn
PATENT ASSIGNEE(S): Cyclops h.f., Iceland
SOURCE: U.S., 31 pp. Cont.-in-part of U.S. 5,324,718.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5472954	A	19951205	US 1994-240510	19940511
US 5324718	A	19940628	US 1992-912853	19920714
EP 579435	A1	19940119	EP 1993-305280	19930706
EP 579435	B1	19990317		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

PRIORITY APPLN. INFO.: US 1992-912853 19920714

EP 1993-305280 19930706

AB The invention provides a method for enhancing the complexation of a **cyclodextrin** with a lipophilic and/or **water**-labile active ingredient which is a drug, cosmetic additive, food additive or agrochem., comprising combining from about 0.1 to about 70% (wt./vol.) of a **cyclodextrin**, from about 0.001 to about 5% (wt./vol.) of a pharmacol. inactive **water**-sol. polymer acceptable for use in a pharmaceutical, cosmetic, food or agricultural compn., and said lipophilic and/or **water**-labile active ingredient in an **aq**. medium, the polymer and **cyclodextrin** being dissolved in the **aq**. medium before the active ingredient is added, the **aq**. medium which comprises the polymer and **cyclodextrin** being maintained at 30-150.degree. for 0.1-100 h before, during and/or after the active ingredient is added, optionally followed by removal of **water**. Related methods, co-complexes of active ingredient/**cyclodextrin**/polymer, pharmaceutical, cosmetic, food and agricultural compns. and **cyclodextrin**/polymer complexing agents are also provided.

L22 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:454268 CAPLUS
DOCUMENT NUMBER: 122:298838
TITLE: Preparation and characterization of **metronidazole** benzoate-.gamma.-**cyclodextrin** inclusion compound
AUTHOR(S): Giordano, F.; Bruni, G.; Abdel Hadi, Ismail; Kata, Mihaly; Gazzaniga, A.; Bettinetti, G.
CORPORATE SOURCE: Dipartimento di Chemica Farmaceutica, Univ. di Pavia, Pavia, 27100, Italy
SOURCE: Bollettino Chimico Farmaceutico (1992), 131(4), 150-6
CODEN: BCFAAI; ISSN: 0006-6648
PUBLISHER: Societa Editoriale Farmaceutica
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Metronidazole** benzoate, an antiprotozoal drug, forms a 1:1 (mol/mol) inclusion compd. with .gamma.-**cyclodextrin**. Phase-**soly**. anal., differential scanning calorimetry, x-ray diffraction on powder, and IR spectra were used in order to characterize the inclusion compd. both in soln. and in solid state. The stability of the drug to alk. hydrolysis was improved in **aq**. solns. of .gamma.-**cyclodextrin**.

L22 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:517696 CAPLUS
DOCUMENT NUMBER: 121:117696
TITLE: Derivatives of **cyclodextrins** exhibiting enhanced **aqueous solubility** and the use thereof
INVENTOR(S): Stella, Valentino J.; Rajewski, Roger
PATENT ASSIGNEE(S): University of Kansas, USA
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9402518	A1	19940203	WO 1993-US6880	19930726
W: AU, CA, JP, KR, RU				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 06511513	T2	19941222	JP 1992-504678	19920726
US 5376645	A	19941227	US 1992-918702	19920727
EP 620828	A1	19941026	EP 1993-918302	19930726
EP 620828	B1	20020508		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AU 672814	B2	19961017	AU 1993-47799	19930726
AU 9347799	A1	19940214		
AT 217325	E	20020515	AT 1993-918302	19930726

PRIORITY APPLN. INFO.: US 1992-918702 A 19920727
US 1990-469087 A2 19900123
WO 1993-US6880 W 19930726

OTHER SOURCE(S): MARPAT 121:117696
AB Sulfoalkyl ether **cyclodextrin** derivs. and their use as **solubilizing** agents for **water** insol. drugs for oral, intranasal, or parenteral administration are disclosed. For example, .beta.-**cyclodextrin** sulfopropyl ether (7 substituents per

cyclodextrin mol.) was prepd. and assocn. consts. for the equil. between the sulfopropyl derivs. and drugs, i.e. digoxin, progesterone, testosterone, and phenytoin were studied.

L22 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:253358 CAPLUS
DOCUMENT NUMBER: 120:253358
TITLE: **Cyclodextrin** complexes with polymers, drugs, agrochemicals and cosmetics
INVENTOR(S): Loftsson, Thorsteinn
PATENT ASSIGNEE(S): Iceland
SOURCE: Eur. Pat. Appl., 46 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 579435	A1	19940119	EP 1993-305280	19930706
EP 579435	B1	19990317		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 5324718	A	19940628	US 1992-912853	19920714
AT 177647	E	19990415	AT 1993-305280	19930706
ES 2132190	T3	19990816	ES 1993-305280	19930706
US 5472954	A	19951205	US 1994-240510	19940511

PRIORITY APPLN. INFO.: US 1992-912853 19920714
EP 1993-305280 19930706

AB A method for enhancing the complexation of a **cyclodextrin** (I) with a lipophilic and/or **water**-labile drug, comprising combining .apprx.0.1-70% (wt./vol.) of I and .apprx.0.001-5% (wt./vol.) of a **water**-sol. polymer in an **aq**. medium. The polymer and I are dissolved in the **aq**. medium before the drug is added. To a soln. contg. Na CM-cellulose 0.25 and 2-hydroxypropyl-.beta.-**cyclodextrin** 10% was added acetazolamide (II) and the soln. was heated at 120.degree. for 20 min and allowed to equilibrate at room temp. for 3 days and amt. of II was detd. The **soly**. of II was 3.11mg/mL as compared to 0.7 for control contg. only II. Different formulations contg. **cyclodextrin** complexes with polymers and drugs are disclosed.

L22 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:589787 CAPLUS
DOCUMENT NUMBER: 115:189787
TITLE: Derivatives of **cyclodextrins** exhibiting enhanced **aqueous solubility** and the use thereof
INVENTOR(S): Stella, Valentino; Rajewski, Roger
PATENT ASSIGNEE(S): University of Kansas, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9111172	A1	19910808	WO 1991-US326	19910122
W: AU, CA, JP, KR, SU				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
US 5134127	A	19920728	US 1990-469087	19900123
CA 2074186	AA	19910724	CA 1991-2074186	19910122
AU 9172364	A1	19910821	AU 1991-72364	19910122
AU 646020	B2	19940203		
EP 512050	A1	19921111	EP 1991-903891	19910122
EP 512050	B1	19980909		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05504783	T2	19930722	JP 1991-504051	19910122
JP 2722277	B2	19980304		
AT 170742	E	19980915	AT 1991-903891	19910122
RU 2099354	C1	19971220	RU 1992-5052811	19920722

PRIORITY APPLN. INFO.: US 1990-469087 A 19900123
WO 1991-US326 A 19910122

OTHER SOURCE(S): MARPAT 115:189787

AB **Cyclodextrin** sulfoalkyl ethers (Markush given) are prepd. as clathrating agents to enhance the **water soly**. of

drugs. A mixt. contg. .beta.-**cyclodextrin** 5, NaOH 2 g, and 10 mL **water** was treated with 4.5 mL of butane sultone and the resulting soln. was neutralized with 1 N HCl to give sulfobutyl ether of .beta.-**cyclodextrin**. The product exhibited no observable toxic effects in mice over a 30 day period following i.p. injection of 0.00549 mol/kg.

L22 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:446267 CAPLUS
DOCUMENT NUMBER: 113:46267
TITLE: Pharmaceutical formulations for parenteral use containing **cyclodextrins** and dihydropyridine redox systems
INVENTOR(S): Bodor, Nicholas S.
PATENT ASSIGNEE(S): University of Florida, USA
SOURCE: Eur. Pat. Appl., 125 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 335545	A2	19891004	EP 1989-302719	19890320
EP 335545	A3	19900926		
EP 335545	B1	19930609		
EP 335545	B2	19980923		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 4983586	A	19910108	US 1988-174945	19880329
EP 327766	A2	19890816	EP 1988-312016	19881219
EP 327766	A3	19900926		
EP 327766	B1	19980408		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 90200	E	19930615	AT 1989-302719	19890320
AU 8931762	A1	19890727	AU 1989-31762	19890328
AU 618995	B2	19920116		
CA 1336498	A1	19950801	CA 1989-594911	19890328
JP 02009825	A2	19900112	JP 1989-77938	19890329
JP 2643426	B2	19970820		
ZA 8902315	A	19901228	ZA 1989-2315	19890329
US 5017566	A	19910521	US 1989-431222	19891103
US 5024998	A	19910618	US 1989-448655	19891211

PRIORITY APPLN. INFO.:
US 1988-174945 A 19880329
EP 1988-312016 A 19881219
US 1987-139755 A2 19871230
CA 1988-585791 A 19881213
IE 1988-3717 A 19881213
IE 1989-810 A 19890314
EP 1989-302719 A 19890320
US 1989-431222 A2 19891103

AB **Aq**. parenteral solns. of drugs which are insol. or only sparingly sol. and/or which are unstable in **water**, are combined with a **cyclodextrin** deriv. to provide a means for alleviating problems assocd. with drug pptn. at the injection site and/or in the lungs or other organs following parenteral administration. Another approach is use of the dihydropyridine-pyridinium redox delivery system. A large no. of examples are given for synthesis of dihydropyridine and pyridinium derivs. of drugs. Data are also presented showing drug **solubilization** by **cyclodextrin** derivs.

L22 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:536904 CAPLUS
DOCUMENT NUMBER: 101:136904
TITLE: Inclusion complexation of **metronidazole** benzoate with .beta.-**cyclodextrin** and its depression of anhydrate-hydrate transition in **aqueous** suspensions
AUTHOR(S): Andersen, Finn M.; Bundgaard, Hans
CORPORATE SOURCE: Dep. Pharm. Chem., R. Dan. Sch. Pharm., Copenhagen, DK-2100, Den.
SOURCE: International Journal of Pharmaceutics (1984), 19(2), 189-97
CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Metronidazole** benzoate (I) [13182-89-3] formed an inclusion complex with .beta.-**cyclodextrin** (.beta.-CyD) in **aq**.

soln. and in the solid phase. A phase **soly**. diagram was obtained and an apparent 1:1 formation complex const. of 1.3 .times. 103 M-1 was detd. A microcryst. inclusion complex had the stoichiometric compn. of 1:1.5 (drug-.beta.-CyD). By inclusion complexation of the I with .beta.-CyD the phase transition of the clin. used anhyd. form of the compd. to the monohydrate, occurring in **aq**. suspensions, was inhibited as was the marked crystal growth resulting from the phase transition. Besides increasing the phys. stability of I suspensions, complexation with .beta.-CyD protected the drug against photochem. degrdn. and decreased the rate of hydrolysis.

L22 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1984:180054 CAPLUS
DOCUMENT NUMBER: 100:180054
TITLE: **Solubilization** of **metronidazole** by **water**-miscible multi-cosolvents and **water**-soluble vitamins
AUTHOR(S): Chien, Yie W.
CORPORATE SOURCE: Coll. Pharm., Rutgers Univ., Piscataway, NJ, USA
SOURCE: Journal of Parenteral Science and Technology (1984), 38(1), 32-6
CODEN: JPATDS; ISSN: 0279-7976
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the systemic treatment of anaerobic infections, parenteral administration of **metronidazole** (I) [443-48-1] is preferable. The practical way of administering a parenteral dose (500 mg) of I in a single 10-mL form can be achieved by incorporating .gtoreq.2 **water**-miscible cosolvents, e.g., ethanol [64-17-5], N,N-dimethylacetamide [127-19-5], propylene glycol [57-55-6], or solketal [100-79-8], into the **aq**. soln. The **aq**. **soly**. of I increased exponentially with increasing vol. fraction of the cosolvents. A max. **soly**. of I was obsd. in **aq**. solns. with a dielec. const. of 41.49. The importance of dielec. const. in detg. the **aq**. **soly**. of slightly **water**-sol. I, which consists of lipophilic and hydrophilic functional groups, is discussed. The **aq**. **soly**. of I can also be enhanced by **solubilizing** with a **water**-sol. vitamin, e.g., **nicotinamide** [98-92-0], ascorbic acid [50-81-7], or pyridoxine-HCl [58-56-0]. A cage-like structure was postulated to rationalize the observation that 9 mols. of vitamins are required to **solubilize** every mol. of I in the **aq**. soln.

L22 ANSWER 12 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95257734 EMBASE
DOCUMENT NUMBER: 1995257734
TITLE: Bioactivation of dinitrobenzamide mustards by an E. Coli B nitroreductase.
AUTHOR: Anlezark G.M.; Melton R.G.; Sherwood R.F.; Wilson W.R.; Denny W.A.; Palmer B.D.; Knox R.J.; Friedlos F.; Williams A.
CORPORATE SOURCE: Ctre. Applied Microbiology/Research, Porton Down,Salisbury, Wilts SP4 0JG, United Kingdom
SOURCE: Biochemical Pharmacology, (1995) 50/5 (609-618).
ISSN: 0006-2952 CODEN: BCPCA6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A nitroreductase isolated and purified from Escherichia coli B has been demonstrated to have potential applications in ADEPT (antibody-directed enzyme prodrug therapy) by its ability in vitro to reduce dinitrobenzamides (e.g. 5-aziridinyl 2,4-dinitrobenzamide, CB 1954 and its bischloroethylamino analogue, SN 23862) to form cytotoxic derivatives. In contrast to CB 1954, in which either nitro group is reducible to the corresponding hydroxylamine, SN 23862 is reduced by the nitroreductase to form only the 2-hydroxylamine. This hydroxylamine can react with S-acetylthiocholine to form a species capable of producing interstrand crosslinks in naked DNA. In terms of ADEPT, SN 23862 has a potential advantage over CB 1954 in that it is not reduced by mammalian DT diaphorases. Therefore, a series of compounds related to SN 23862 has been synthesized, and evaluated as potential prodrugs both by determination of kinetic parameters and by ratio of IC50 against UV4 cells when incubated

in the presence of prodrug, with and without the E. coli enzyme and cofactor (NADH). Results from the two studies were generally in good agreement in that compounds showing no increase in cytotoxicity in presence of enzyme and cofactor were not substrates for the enzyme. None of the analogues were activated by DT diaphorase isolated from Walker 256 carcinoma cells. For those compounds which were substrates for the E. coil nitroreductase, there was a positive correlation was between k(cat) and IC50 ratio. Two compounds showed advantageous properties: SN 25261 (with a dihydroxypropylcarboxamide ring substituent) which has a more than 10-fold greater **aqueous solubility** than SN 23862 whilst retaining similar kinetic characteristics and where a change in the position of the carboxamide group relative to the cytotoxicity ratio and k(cat) compared with SN 23862 (IC50 ratios 214 26.4 sec-1, respectively). An analogue (SN 25507) incorporating both enhanced k(cat) of 576 sec-1. This study elucidates some of the structural aids identification of further directions in the search for suitable prodrugs system.

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ACCESSION NUMBER: 2002:622097 BIOSIS
DOCUMENT NUMBER: PREV200200622097
TITLE: Gel compositions containing **metronidazole**.
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ASSIGNEE: Dow Pharmaceutical Sciences
PATENT INFORMATION: US 6468989 October 22, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Oct. 22, 2002) Vol. 1263, No. 4, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB An **aqueous** solution of **metronidazole** in which the concentration of **metronidazole** is higher than 0.75%. The solution contains the **solubility** enhancer hydroxypropyl-betacyclodextrin and may additionally contain **niacinamide**. Methods of manufacture and therapeutic use of the solution are disclosed.